IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent Application	Group Art Unit: 1609
Jonathan S. STAMLER, et al.	Confirmation No.: 6780
Application Number: 10/508,957	Attny Dkt No.: STAM3022/ESS/PAD
Filed: February 3, 2005	Examiner: G. G. Huang

For: METHOD AND COMPOSITIONS BASED ON DISCOVERY OF METABOLISM OF NITROGLYCERIN

REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is submitted in response to the Examiner's Answer of April 3, 2009. The Reply Brief is due by June 3, 2009. The Reply Brief has been timely filed.

Appellants respectfully submit that the rejections of claims 75-84 set forth in the Examiner's Answer are improper and should be reversed in view of the Appeal Brief filed on December 5, 2008 and in light of the remarks that follow:

The claimed invention is based on Appellants discovery that biotransformation of nitroglycerin occurs predominately in mitochondria through a previously unknown reductase action of the known enzyme mitochondrial aldehyde dehydrogenase (mtALDH, ALDH2) and that attenuated biotransformation of nitroglycerin by mtALDH underlies nitrate tolerance (page 2, lines 20-30).

Claim 74 is a method for activating inactivated mtALDH in a patient who has received nitroglycerin therapy and has become nitroglycerin tolerant so the patient no longer responds to nitroglycerin. Claim 84 is a method for restoring clinical sensitivity to nitroglycerin to a patient who has lost sensitivity to nitroglycerin so that the patient no longer responds to nitroglycerin.

Appellants have carefully reviewed the Examiner's Answer and respectfully submit that the rejections of the Examiner's Answer are based on an unreasonable interpretation of the claims.

I. CLAIMS 75-84 SATISFY THE WRITTEN DESCRIPTION REQUIREMENT PURSUANT TO 35 U.S.C. 112, FIRST PARAGRAPH

This rejection is improper as a matter of law. The Patent Office has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97. However, the Examiner's Answer fails to provide any evidence in support of this rejection.

For example, the Examiner's Answer contends that Examples XXXII and XXXIII do not support the recitation "no longer responsive to nitroglycerin", despite the fact that these examples relate to reversing nitroglycerin tolerance in a patient that has been undergoing nitroglycerin therapy. Rather, the Examiner's Answer unilaterally interprets the phrase as meaning that the patient is "completely" tolerant and holds that Examples XXXII and XXXIII merely show potentiating nitroglycerin tolerance as the degree of tolerance is not characterized in terms of its clinical effect (Examiner's Answer, page 17, lines 15-20). In light of the lack of evidence, Appellants respectfully submit that the rejection is improper and must be reversed.

Nevertheless, Appellants note that support for the claimed invention is found in the present specification at page 2, line 23 to page 3, line 17; page 11, lines 10-20; and page 13, lines 5-15. At page 11, lines 10-20, the specification discusses the difference between potentiating tolerance and reversing tolerance. Examples XXXII and XXXIII on page 45 also provide support for the claimed invention.

The phrase "nitroglycerin sensitivity restoring amount" is supported at page 11, line 20 to page 12, line 20 of the specification. In addition, Background Example 4 beginning on page 37 of the specification discusses dosages for the compounds recited in claims 75 and 84. The results of Background Example 4 are shown in Figure 1. Thus, specific dosages for DTT, DHLA and TCEP are provided in the specification. Examples XXXII and XXXIII on page 45 show restoring sensitivity to nitroglycerin in a patient.

As noted above, Appellants are the first to discover that the biotransformation of nitroglycerin occurs predominantly in mitochondria through a previously unknown reductase action of mtALDH and that attenuated biotransformation of nitroglycerin by mtALDH underlies nitrate tolerance. In this regard, one skilled in the art would consider the teachings of the present specification and figures within this context. Upon considering the claims as a whole and reviewing the specification in full, one skilled in the art would recognize that Appellant was in possession of the claimed invention as a whole at the time of filing.

Contrary to the contentions of the Examiner's Answer at the bottom of page 13, an invention need not be described *ipsis verbis* in the specification in order to satisfy the disclosure requirements.

II. CLAIMS 75-84 SATISFY THE ENABLEMENT REQUIREMENT PURSUANT TO 35 U.S.C. 112, FIRST PARAGRAPH

The invention is independent of the disease for which nitroglycerin is administered and is directed to restoring clinical sensitivity to nitroglycerin to a patient who has lost clinical sensitivity to nitroglycerin (see claims 75 and 84). A condition not capable of being treated by nitroglycerin is not encompassed by the claims. Furthermore, claims 75 and 84 certainly do not give the Examiner's Answer the license to interpret the claims as encompassing any and all disorders. Accordingly, Appellants respectfully submit that the Examiner's interpretation of the claims is unreasonable and must be withdrawn.

The publications cited by the Examiner's Answer such as Kennedy, T., et al., *JAMA* 246(2) and the Physicians Desk Reference are irrelevant for purposes of determining whether the claimed invention satisfies the enablement requirement. Appellants neither claim nor contend that nitroglycerin is capable of treating any and all conditions. Indeed, the documents merely evidence that one skilled in the art would know what conditions could be treated with nitroglycerin.

Nevertheless, even if the documents were considered relevant, Appellants note that in the Amendment of January 9, 2008 on page 6 that since the publication of the Kennedy, T., et al., *JAMA* 246(2) article, others have found that nitroglycerin provides a benefit for asthma and cited to Rolla, G., et al., *Pulmonary Pharmacology* 1995, April – June, 8(2-3):137-141 and Sharara, A.M., et al., *Pulmonary Pharmacology and Therapeutics* 11(1), 65-70 (February 1998).

III. CLAIMS 75-78, 81, AND 84 ARE NOT ANTICIPATED UNDER 35 U.S.C. 102 BY WEISCHER ET AL.

Appellants acknowledge the newly imposed rejection, wherein claim 84 is rejected as allagdly being anticipated by WEISHCER. Appellants traverse this rejection and request that this appeal be maintained.

WEISCHER never administers the disclosed preparation to a patient no longer responsive to nitroglycerin (WEISCHER, translation by Schreiber Translation, Inc., pg. 3, lines 1-10). WEISCHER describes that the preparation is based on a synergistic effect (See page 6, third full paragraph). For example, as indicated in the results section of WEISCHER, nitroglycerin plus alpha-lipoic acid gives a stronger effect than alpha-lipoic acid alone (page 7, line 15-20).

Thus, WEISCHER makes every effort to prevent the patient from falling into a state, wherein the patient is no longer responsive to nitroglycerin. While Weischer may suggest preventing nitroglycerin tolerance from occurring, WEISCHER does not necessarily or inherently show that nitroglycerin tolerance can be reversed or postponed.

Even if it is considered that WEISCHER potentiates a response, potentiation does not mean restoring clinical sensitivity in the claimed milieu. For example, N-acetylcysteine potentiates the effect of nitroglycerin, but does not restore clinical sensitivity to nitroglycerin to a patient who has lost such sensitivity. See Loscalzo, *J., J. Clin. Invest.* 76(2), 703-708 (8/85). Thus, the potentiation effect taught by WEISCHER does not necessarily provide a reasonable expectation of success for the sensitivity restoration effect recited in the claims.

The Examiner's Answer cites to pages 1-2, Table 1, and claim 21 of the EPO machine translation in support of the anticipation rejection. Appellants are not sure why the Examiner's Answer does not refer to the translation provided by the Patent Office, but note that neither translation discloses that the WEISCHER preparation was administered to a patient that has become nitroglycerin tolerant.

IV. CLAIMS 75-83 ARE NOT OBVIOUS OVER WEISCHER AND PRUIJN.

PRUIJN studies the relationship between vitamin E, glutathione and dihydrolipoic acid in protecting against lipid peroxidation. PRUIJN does not disclose or suggest activating inactivated mtALDH, or even administering DTT to overcome

nitroglycerine tolerance in a patient. Thus, PRUIJN fails to remedy the deficiencies of WEISCHER for reference purposes.

V. CLAIMS 75-83 ARE NOT OBVIOUS OVER WEISCHER, PRUIJN AND GETZ

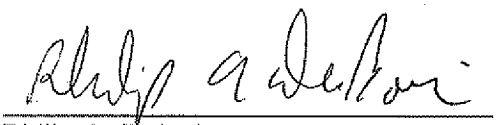
GETZ compares the properties of DTT and TCEP (page 73, left column, lines 1-10), but neither discloses nor suggests activating inactivated mtALDH, or overcoming nitroglycerin tolerance in a patient. Accordingly, GETZ fails to remedy the deficiencies of PRUIJN and GETZ.

VI. CONCLUSION

From the foregoing discussion, it is believed that the rejections of claims 75-84 are improper and should be reversed.

Appellants do not believe that any fees are due at this time. However, the Patent Office is authorized to charge any required to Deposit Account No. 02-200.

Respectfully submitted,
BACON & THOMAS, PLLC

By: 
Philip A. DuBois
Registration No. 50,696

625 Slaters Lane, 4th Fl.
Alexandria, Virginia 22314
Phone: (703) 683-0500
Facsimile: (703) 683-1080
Appeal Brief.doc
PAD/amg